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Update on "Drug Metabolism/Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling"

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Draft Drug Interaction Guidance (in internal review)-

- **To replace two metabolism/drug interaction guidance documents published in 1997 and 1999**

- *http://www.fda.gov/cder/guidance/2635fnl.pdf*
- *http://www.fda.gov/cder/guidance/clin3.pdf*

- **To update and include recent findings and discussions from conferences and publications**

- *Tucker, Houston and Huang, Clin Pharm Ther August 2001; 70(2):103*
- *Yuan, Madani, Wei, Reynolds, Huang, Drug Metab Disp, December 2002; 30(12) 1311*
- *Bjornsson, Callaghan, Einolf, et al, J Clin Pharmacol, May 2003; 43(5):443*
- *Huang, Lesko, J Clin Pharmacol, June 2004; 44: 559*

- **To address recent labeling rule changes**

- *Labeling guideline. Federal Register 65[247], 81082-81131. December 22, 2000.*
  - Draft guidance for industry "Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements" and "clinical pharmacology and drug interaction labeling guidance" (in internal review)

Key messages:

1. **Metabolism, drug-interaction info key to benefit/risk assessment**
2. **Integrated approach may reduce number of unnecessary studies and optimize knowledge**
3. **Study design/data analysis key to important information for proper labeling**
4. **Need to establish "Therapeutic equivalence boundaries"**

Recent US Market Withdrawal

Withdrawn	Approval	Drug name	Use	Risk
1998	1997	Mibefradil	High blood pressure/ Chronic stable angina	Drug-drug interactions Torsades de Pointes
1998	1997	Bromfenac	NSAID	Acute liver failure
1998	1985	Terfenadine	Antihistamine	Torsades de Pointes Drug-drug interactions
1999	1988	Astemizole	Antihistamine	Torsades de Pointes Drug-drug interactions
1999	1997	Grepafloxacin	Antibiotics	Torsades de Pointes
				Ischemic colitis; complications of constipation
				Torsades de Pointes Drug-drug interactions
				Acute liver failure
2001	1997	Cerivastatin	Cholesterol lowering	Rhabdomyolysis Drug-drug interactions
2001	1999	Rapacuronium	Anesthesia	Bronchospasm

Need to evaluate other drug's effects on NME and the NME's effects on other drugs

Huang SM, Miller M, Toigo T, Chen MC, Sahajwala C, Lesko LJ, Temple R, Evaluation of Drugs in Women: Regulatory Perspective– in Section 11, Drug Metabolism/Clinical Pharmacology (section editor: Schwartz, J), in "Principles of Gender-Specific Medicine", Ed., Legato M, Academic Press (2004) .

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In vitro evaluations using human tissues can eliminate the need or prioritize in vivo evaluation in humans

Design the in vivo evaluation based on in vitro data (evaluate the most potent one, smallest Ki, first)

Cmax of NME 1 uM

	IC50	Ki
CYP1A2	50 uM	40 uM
CYP2C9	20uM	10 uM
CYP2C19	>100 uM	--
CYP2D6	>100 uM	--
CYP3A4	7uM	2 uM

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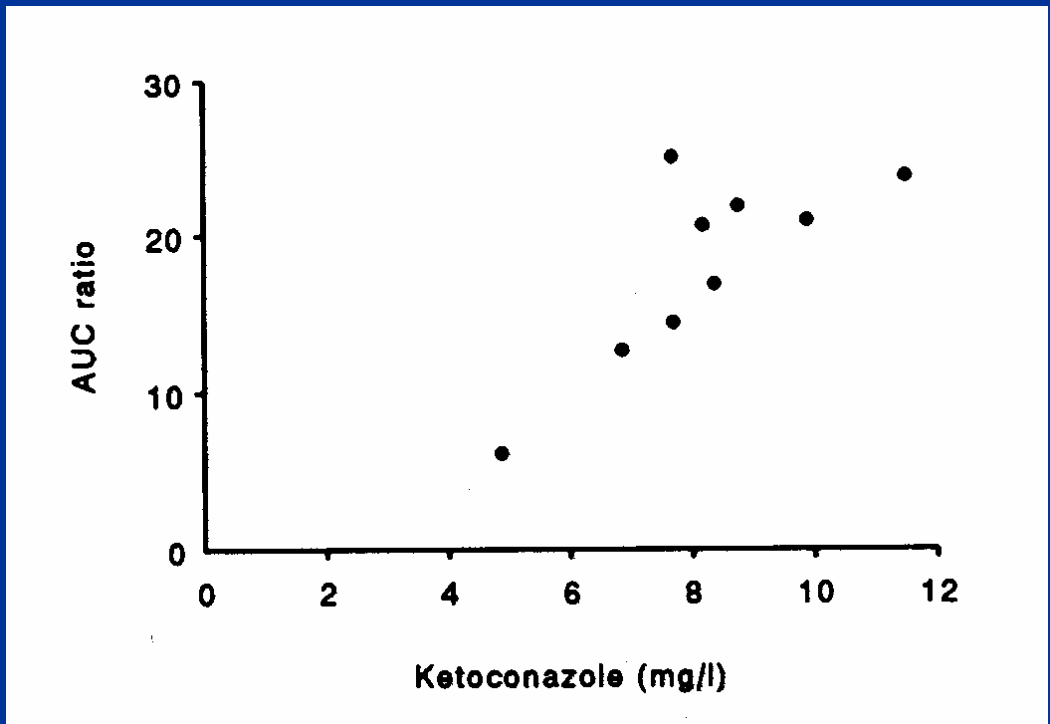
Design a study to maximize seeing an interaction

Why high dose inhibitor?
- 400 mg vs. 200 mg of ketoconazole -

Midazolam (keto)/Midazolam (placebo)
Midazolam at 7.5 mg

1. In house data
2. Literature data



Olkkola et al., CPT 55:481, 1994

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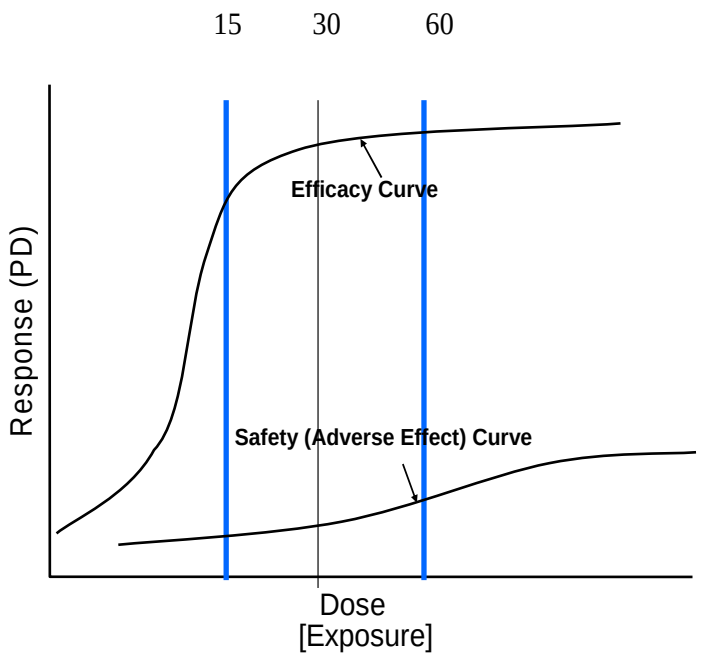
Drug B - CYP3A substrate

Drug B with	Drug B AUC	Drug B Cmax
Ketoconazole	6x	4x
Erythromycin	4x	3x
Verapamil	4x	3x

[approved]



Do not take with potent CYP3A inhibitors….
Ketoconazole, itraconazole, TAO, ritonavir, nelfinavir, nefazodone, clarithromycin.

Use lower doses with moderate CYP3A inhibitors…..
erythromycin, verapamil, diltiazem...

Drug Interaction Guidance Revision (in internal review)-

- **Recommendation of probe substrates, inhibitors, inducers in tables**

- **Discussion of in vitro evaluation**

- **Discussion of labeling implication**
(strong and moderate CYP3A inhibitors; sensitive or NTR CYP3A substrates)

- **Others**

In vivo probes

CYP	Substrate	Inhibitor	Inducer
1A2	theophylline, caffeine	fluvoxamine	Omeprazole? smoking[3]
2B6	efavirenz		rifampin nevirapine ?
2C8	repaglinide, rosiglitazone	gemfibrozil	rifampin
2C9	warfarin, tolbutamide	fluconazole, amiodarone (use of PM subjects) [4]	rifampin
2C19	omeprazol, esoprazol, lansoprazol, pantoprasol	omeprazole, fluvoxamine, moclobemide (use of PM subjects) [4]	rifampin
2D6	desipramine, atomoxetine dextromethorphan,	paroxetine, quinidine, (use of PM subjects) [4]	None identified
2E1	chlorzoxazone	disulfirum	ethanol
3A4/ 3A5	midazolam, buspirone, felodipine, simvastatin, Lovastatin, eletriptan, sildenafil, simvastatin, triazolam	atanazavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin,	rifampin, rifabutin, rifapentin, phenytoin, phenobarbita

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- **Discussion of labeling implication (strong and moderate CYP3A inhibitors; sensitive or NTR CYP3A substrates)**

- **Others**

In vitro evaluation

- **Detailed discussion on issues to consider in reviewing studies**
  - **to elucidate the metabolic pathways**
  - **to assess inhibition potential**
  - **to assess induction potential**
- **General study design issues**
  - **recommendation of probe substrates, inhibitors, inducers in tables**

Evaluation of induction

- **issues may be addressed in *in vivo* studies evaluating inhibition**

- **initial *in vitro* evaluation with 2 CYPs (CYP1A2, CYP3A)**

- negative results may preclude in vivo evaluation of CYP1A2, CYP3A, CYP2C9, CYP2C19

- positive control recommended

- 40% of positive control or 2-fold increase over negative control suggest possible induction potential -> follow with *in vivo* evaluation

Drug Interaction Guidance Revision (in internal review)-

- **Recommendation of probe substrates, inhibitors, inducers in tables**

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- **Discussion of labeling implication (strong and moderate CYP3A inhibitors; sensitive or NTR CYP3A substrates)**

- **Others**

- **Examples of sensitive CYP3A substrates or CYP3A substrates with NTR**

if a drug has been determined to be a strong inhibitor of CYP3A, it does not need to be tested with all CYP3A substrates to warn about an interaction with “sensitive CYP3A substrates” and “CYP3A substrates with narrow therapeutic range”.

Drug Interaction Guidance Revision (in internal review)-

- **Examples of sensitive CYP3A substrates or CYP3A substrates with NTR**

Sensitive CYP3A substrates	CYP3A Substrates with Narrow therapeutic range
budesonide, buspirone, eletriptan, felodipine, imatinab, lovastatin, midazolam, saquinavir, sildenafil, simvastatin, triazolam	Alfentanil, astemizole(a), cisapride(a), cyclosporine, diergotamine, ergotamine, fentanyl, irinotecan, pimozide, quinidine, sirolimus, tacrolimus, terfenadine(a)

- **Examples of strong and moderate CYP3A inhibitors**

If a drug has been determined to be a sensitive CYP3A substrate or a CYP3A substrate with a narrow therapeutic range, it does not need to be tested with all strong or moderate inhibitors of CYP3A to warn about an interaction with "strong" or "moderate" CYP3A inhibitors

• Examples of strong and moderate CYP3A inhibitors

Strong CYP3A inhibitors	Moderate CYP3A inhibitors
atanazavir clarithromycin cyclosporine? delavirdine? indinavir itraconazole ketoconazole nefazodone nelfinavir ritonavir saquinavir telithromycin TAO	Amprenavir aprepitant diltiazem erythromycin fluconazole fosaprenavir grapefruit juice(a) verapamil

Drug Interaction Guidance Revision (in internal review)-

- **Recommendation of probe substrates, inhibitors, inducers in tables**

- **Discussion of in vitro evaluation**

- **Discussion of labeling implication (strong and moderate CYP3A inhibitors; sensitive or NTR CYP3A substrates)**

- **<u>Others</u>**

- **discussed PK evaluation in poor metabolizers (PM) or smokers in lieu of certain interaction studies**
  - ***Evaluation interaction based on one pathway in PM of the enzyme for another pathway***

- **discussed protocol exclusion criteria to address possible herb-drug, juice-drug interactions**

- **discussed use of multiple inhibitors/ multiple impaired system when evaluating QT changes**

- **discussed P-gp transporter based interaction**

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4. Need to establish “Therapeutic equivalence boundaries”

Drug Interactions working group

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